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EFFECTS OF IBOGAINE ON ACUTE SIGNS OF MORPHINE WITHDRAWAL IN RATS: INDEPENDENCE FROM TREMOR

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Summary—Because of the claim that ibogaine suppresses the symptoms of “narcotic withdrawal” in humans, the effect of ibogaine on naltrexone-precipitated withdrawal signs in morphine-dependent rats was assessed. Morphine was administered subcutaneously through implanted silicone reservoirs for 5 days. Ibogaine (20, 40 or 80 mg/kg, i.p.) or saline was administered 30 min prior to challenge with naltrexone (1 mg/kg, i.p.) and withdrawal signs were counted for the following 2 hr. Ibogaine (40 and 80 mg/kg) significantly reduced the occurrence of four signs (wet-dog shakes, grooming, teeth chattering and diarrhea) during naltrexone-precipitated withdrawal; three other signs (weight loss, burying and flinching) were unaffected. Ibogaine induces head and body tremors lasting for 2–3 hr and the tremors might have interfered with the expression of opioid withdrawal. To examine this issue, another experiment was conducted in which ibogaine (40 mg/kg) or saline was administered 4 hr prior to challenge with naltrexone. Although there was a complete absence of tremors, ibogaine still significantly reduced the occurrence of the same four signs of withdrawal.

Key words—ibogaine, morphine, dependence, withdrawal.

It has been claimed (H. Lotsof, NDA International Inc.) that ibogaine, an alkaloid found in the root bark of the African shrub *Tabernanthe iboga*, will “interrupt the physiological and psychological aspects of the opiate addiction syndrome” (U.S. patent number 4,499,096) and “suppress the multiple symptoms and physical discomfort of narcotic withdrawal” (ENDABUSETM product information). In attempts to examine this claim, three studies have assessed the effects of ibogaine on withdrawal signs in morphine-dependent animals. The results have been inconsistent. Dzoljic, Kaplan and Dzoljic (1988) reported that intracerebroventricular (i.c.v.) administration of ibogaine attenuated many but not all signs of naloxone-precipitated withdrawal in morphine-dependent rats. In a study sponsored by the Committee on Problems of Drug Dependence, Inc., Aceto, Bowman and Harris (1990) reported that subcutaneously (s.c.) administered ibogaine partially suppressed withdrawal signs in morphine-dependent monkeys. However, Sharpe and Jaffe (1990) concluded that subcutaneous administration of ibogaine failed to reduce naloxone-precipitated withdrawal signs in morphine-dependent rats, although they did report that one sign (grooming) of withdrawal was depressed. It was reported that, in rats, intraperitoneally (i.p.) administered ibogaine reduced morphine self-administration behavior (Glick, Rossman, Steindorf, Maisonneuve and Carlson, 1991) and blocked morphine-induced release of dopamine in nigrostriatal and mesocorticolimbic regions of the brain (Maisonneuve, Keller and Glick, 1991). The

present study was conducted to re-examine the possibility that ibogaine might attenuate morphine-withdrawal, using the same dose parameters for ibogaine that had been used previously.

METHODS

Subjects

The subjects were 55 naive male Sprague–Dawley (Taconic, Germantown, New York) rats, approx 3 months old and weighing 230–250 g, at the beginning of the experiment. The rats were housed singly and maintained on a normal light/dark cycle (lights on/off at 7:00 a.m./7:00 p.m.).

Procedure

Morphine was administered subcutaneously for 5 days, through implanted silicone reservoirs, as described by Goode (1971) and as done previously in this laboratory (e.g. Glick, Cox and Crane, 1975). Administration of morphine was begun on the day after implantation of the reservoir; the reservoir was initially filled with 0.5 ml of 50 mg/ml morphine sulfate solution, in a saline vehicle. On each of the next 3–4 days, the reservoirs were rinsed with physiological saline and refilled with the same solution of morphine sulfate. On the withdrawal day, the reservoirs were rinsed and filled only with saline. Ibogaine hydrochloride (20, 40 or 80 mg/kg; Sigma Chemical Company, St Louis, Missouri) or saline (1–4 ml/kg) was then administered intraperitoneally, followed, 30 min later, by intraperitoneal injection of

naltrexonehydrochloride, 1.0 mg/kg. The body weight of each rat was recorded immediately before administration of naltrexone and 2 hr later. Beginning immediately after the injection of naltrexone, the rats were observed continuously for 2 hr and signs of withdrawal were counted: wet-dog shakes, grooming, teeth chattering, flinching/paw shaking, burying and diarrhea were recorded, as the number of incidents of each behavior for each animal, during the 2 hr. A saline-pretreated rat and an ibogaine-pretreated rat were observed simultaneously; observations were made blindly with respect to pretreatment with saline or ibogaine.

Doses of ibogaine ≥ 20 mg/kg induced head and body tremors, lasting 2–3 hr. To control for the possibility that such tremors might interfere with the expression of opioid-induced withdrawal and confound any interpretation of results, two additional groups of rats, one given ibogaine (40 mg/kg) and the other saline (2 ml/kg), were treated exactly as described above, except that the injection of naltrexone and the ensuing precipitation of withdrawal signs were delayed 4 hr.

RESULTS

As shown in Fig. 1, ibogaine significantly (ANOVA and Newman-Keuls' test) decreased the intensity of some but not all signs of acute naltrexone-precipitated withdrawal in morphine-dependent rats. Wet-dog shakes, grooming, teeth chattering and diarrhea were significantly affected. In order to compare the different withdrawal signs and to account for the variability in control data from one day to another, all withdrawal scores were converted to

percentage changes from the appropriate control values (i.e. mean values of saline-treated rats, tested on the same day). Mean ($\pm$ SEM) withdrawal scores of all saline-treated rats ($N = 17$) in the main experiment were as follows: weight loss (g), 19.8 ± 1.3 ; wet-dog shakes, 61.2 ± 10.8 ; grooming, 26.7 ± 4.8 ; burying, 9.1 ± 1.9 ; flinching, 6.4 ± 1.7 ; teeth chattering, 12.3 ± 2.0 ; and diarrhea, 1.9 ± 0.4 .

When administered 4 hr after cessation of administration of morphine, naltrexone still elicited withdrawal signs but of somewhat different severity than when administered 3.5 hr earlier. In the saline-treated group, weight loss (22.8 ± 1.1) and wet-dog shakes (76.4 ± 7.2) were a little greater whereas grooming (13.0 ± 2.2) and teeth chattering (1.8 ± 1.0) were substantially less than the comparable values (see above) of the saline-treated rats, injected with naltrexone earlier ($P < 0.05$, *t*-test for difference in teeth chattering). As shown in Fig. 2, when administered 4 hr prior to naltrexone, ibogaine had effects that were very similar to those (Fig. 1) produced by administering ibogaine 30 min prior to naltrexone: ibogaine significantly decreased the intensity of the same four withdrawal signs and to approximately the same extent.

DISCUSSION

When administered shortly before naltrexone, ibogaine significantly attenuated some signs, i.e. wet-dog shakes, grooming, teeth chattering and diarrhea, of the acute morphine-withdrawal syndrome. There were both similarities and differences between these results and those reported in two previous studies with rats. Sharpe and Jaffe (1990) found that the only

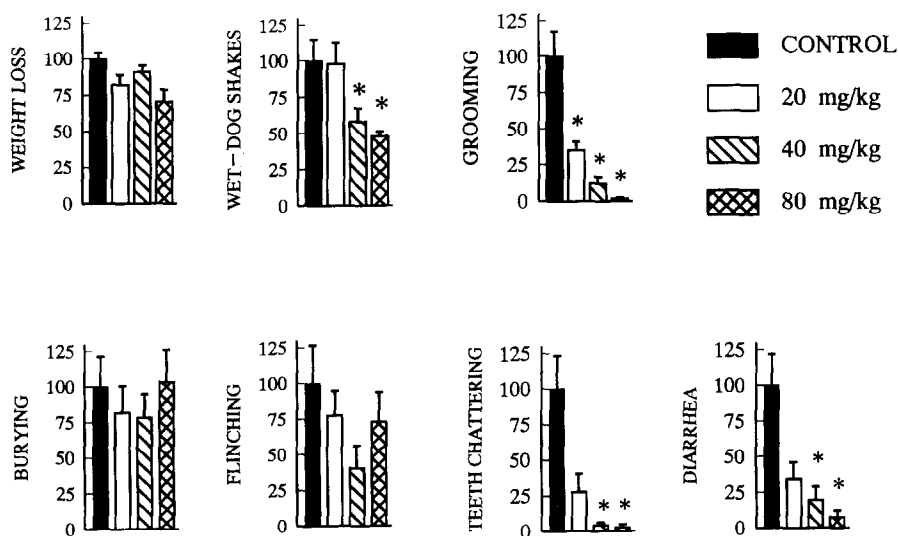


Fig. 1. Effects of ibogaine [20 mg/kg ($N = 7$), 40 mg/kg ($N = 13$) or 80 mg/kg ($N = 7$)] on withdrawal signs. Ibogaine or saline ($N = 17$) was administered immediately after cessation of administration of morphine and 30 min before administration of naltrexone; withdrawal signs were recorded over the following 2 hr. Each value is the mean $\pm$ SEM percentage withdrawal score (% of control mean). Asterisks indicate significant differences between ibogaine and control values (* $P < 0.05$, Newman-Keuls tests).

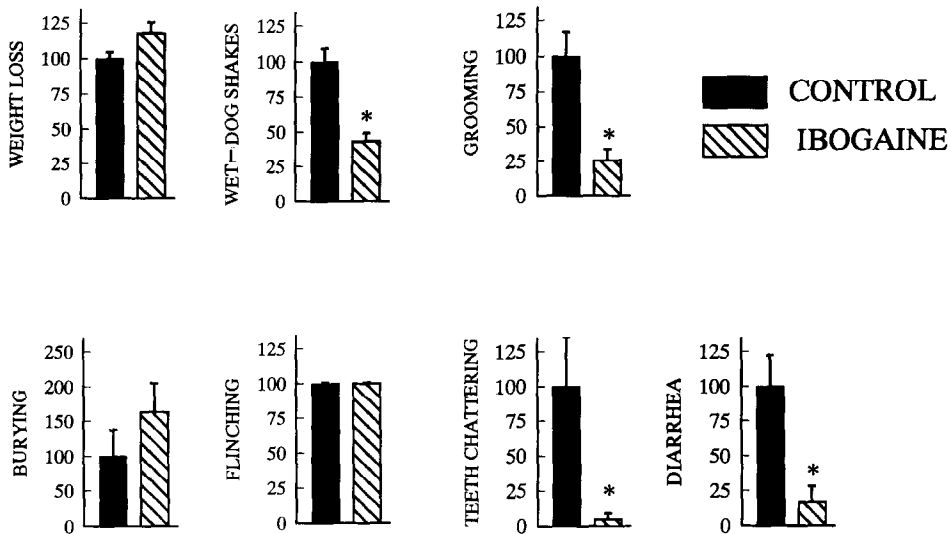


Fig. 2. Effects of ibogaine (40 mg/kg) on withdrawal signs. Ibogaine ($N = 6$) or saline ($N = 5$) was administered immediately after cessation of administration of morphine and 4 hr before administration of naltrexone; withdrawal signs were recorded over the following 2 hr. Each value is the mean $\pm$ SEM percentage withdrawal score (% of control mean). Asterisks indicate significant differences between ibogaine and control values (* $P < 0.05$, t -tests).

withdrawal sign to decrease significantly was grooming, whereas Dzoljic *et al.* (1988) found that grooming was not affected while many other signs, including digging (burying) and teeth chattering, were significantly reduced. As pointed out by Sharpe and Jaffe (1990), such discrepancies may be due to methodological differences. A different procedure for infusion of morphine, a longer period of exposure to morphine and a longer withdrawal test were used in the present study, as compared to the previous studies; 230–250 g male Sprague–Dawley derived (Taconic) rats were used here, whereas Sharpe and Jaffe (1990) used 350–450 g male Sprague–Dawley derived (Harlan) rats and Dzoljic *et al.* (1988) used 190–200 g male Wistar rats. In the present study, ibogaine was administered by the intraperitoneal route, rather than by the subcutaneous (Sharpe and Jaffe, 1990) or intracerebroventricular (Dzoljic *et al.*, 1988) route and withdrawal signs were precipitated by naltrexone (1.0 mg/kg, i.p.), 30 min later, rather than by naloxone (0.5 mg/kg, s.c., Sharpe and Jaffe, 1990; 5.0 mg/kg, i.p., Dzoljic *et al.*, 1988), 15 min later. Despite all of these differences, some aspect of the opiate withdrawal syndrome was ameliorated in all three studies.

It is obvious to most observers that ibogaine induces head and body tremors in rats. This raised two issues regarding the interpretation of the anti-withdrawal effects discussed above. First, it seemed possible that the tremors and the associated motor abnormalities, might have interfered with the expression of the opioid withdrawal signs being measured. And second, although the studies were conducted “blindly”, the occurrence of tremors clearly distinguished ibogaine-treated rats from

saline-treated rats. Ibogaine-induced tremors dissipate within 2–3 hr and are entirely absent within 4 hr. Another experiment was therefore conducted in which ibogaine was administered 4 hr before the injection of naltrexone and the precipitation of withdrawal signs. It was reasoned that if ibogaine specifically affected a mechanism involved in opioid dependence, it might still be effective in attenuating withdrawal signs, 4 hr later; alternatively, as indicated by previous results (Glick *et al.*, 1991; Maisonneuve *et al.*, 1991), ibogaine or possibly an active metabolite, might produce persistent changes in neuronal activity. The results of this experiment were very clear: in the absence of tremors, ibogaine still reduced the occurrence of some withdrawal signs, the same ones affected in the earlier experiments.

Exactly how ibogaine might attenuate opioid withdrawal is, at this point, open to conjecture. There is some evidence that ibogaine may potentiate the actions of morphine (Schneider and McArthur, 1956); the previous findings (see introduction) could also be interpreted in this way (see Glick *et al.*, 1991; Maisonneuve *et al.*, 1991). If, when administered prior to the withdrawal test, ibogaine potentiated the effects of morphine, it might be expected that the ensuing withdrawal signs would be mitigated inasmuch as naltrexone would be competing with persistent agonist actions. It is also of interest that ibogaine has been found to bind to kappa opioid receptors ($K_i = 2.08 \mu\text{M}$; Deecher, Teitler, Soderlund, Bornmann, Kuehne and Glick, 1992) and the anti-withdrawal effects of ibogaine may be attributable to an interaction between kappa- and mu-mediated opioid mechanisms. Regardless of the explanation, the present results indicate that the potential usefulness of

ibogaine in treating the acute manifestations of opioid dependence should be further investigated.

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